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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,581	05/03/2002	Dan L. Eaton	P3230R1C001-168	2389

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EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,581	EATON ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 11-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

Claims 9-10 are canceled. The amendment of claims 1-8 has been made of record.

Claims 1-8, and 11-13 are pending.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

RESPONSE TO AMENDMENT

Priority

Applicants' acknowledgement for the instant application to PCT/US00/23328 filed on 8/24/00 has been entered. Applicants state that the sequences of SEQ ID NOs: 71 and 72 are disclosed in US Provisional 60/096,757 filed on 8/17/1998, however, the claimed invention does not have support in the Provisional application. Therefore, the instant application gets priority of 8/24/2000.

Correction of Inventorship under 37 CFR 1.48 (b)

Applicant's request to correct inventorship under 37CFR 1.48 (b) to remove Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe is acknowledged.

The request for the deletion of an inventor in this nonprovisional application under 37 CFR 1.48(b) is deficient because:

It lacks the required fee under 37 CFR 1.17(i).

Claim Rejections/Objections Withdrawn

The objection to the specification regarding the use of trademarks which were not capitalized and did not include the generic terminology is withdrawn in response to Applicant's amendments to the specification.

The rejection of claim 1 under 35 U.S.C. 102(a) as being anticipated by Osada et al. is withdrawn in view of Applicants' statement for the support in the published PCT/US00/23328 application, and the amendment to the claim. Therefore, the instant application gets the priority of 8/24/2000.

The rejection of claims 12-13 under 35 U.S.C. 103(a) as being unpatentable over Osada as applied to claim 1, and further in view of US Patent No.5, 639,597 is withdrawn due to Applicant's amendment to claim 1 and Applicant's Remarks filed on 7/25/2005 regarding priority of the instant application.

Claim Objections/Rejections Maintained

Claim Rejections - 35 USC § 101

The rejection of claims 1-8, and 11-13 under 35 U.S.C. 101 is maintained for reasons of record on p. 3-4 of the office action mailed on 6/25/2004.

The rejection of claims 1-8, and 11-13 under 35 U.S.C. 112, first paragraph is maintained for reasons of record on p. 4. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims are directed to an isolated polypeptide having at least 80%, 90%, 95%, and 99% amino acid sequence identity to an isolated polypeptide molecules comprising SEQ ID NO: 72. The claimed polypeptides are not supported by either a specific and substantial asserted utility or a well-established utility. Applicants refer *to In re Brana, 51 F.3d 1560* (Fed. Cir. 1995) regarding the expectation of further research and development. Applicants point to the previously submitted Declaration by Polakis, Grimaldi and the Ashkenazi.

Applicant reviews the legal test for utility, with which the examiner takes no issue.

Applicant's response received 25 July 2005 and the Polakis, Grimaldi and the Ashkenazi declaration have been fully considered but they are insufficient to overcome the rejection of claims 72-76 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons:

Applicant argues that the utility of the PRO1287 nucleic acid carries over to the protein and antibody claims. Specifically, Applicant argues that there is an assumption of utility unless a reason for one skilled in the art to question the objective truth of the statement of utility or its scope can be established. Applicant cites case laws in support of this assertion. Applicant urges that a *prima facie* case of lack of utility has not been established. In support to establish a specific, substantial and credible utility Applicants point to examples Ornoft (exhibit 4), Hyman (exhibit 5), and Pollack (exhibit 6) which are array based method. Applicants argue that Ornoft et al describe that a two fold mRNA increase is relevant when looked in relation to gene dosage. Also, Pollack et al suggest that 62% of highly amplified genes show an increase in moderately to high level of

mRNA which is also observed by Hyman et al in a number of breast cancer tumors and cell lines.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, although Ornoft , Hyman and Pollack suggest that in tumors or cancer cell lines differential expression of genes are relevant, but one skilled in the art still cannot determine if the "overexpression" of PRO1287 in Example 12, page 142 of the instant specification is statistically significant because of the lack of qualitative or numerical results. The state of the art is such that the accuracy and biological relevance of data generated from microarray techniques remain controversial. For instance, Bustin et al. (TRENDS in Molec. Med. 8(6): 269-272, 2002) review the numerous issues related to format, quality, validation, and interpretation of microarrays. Bustin et al. teaches that although microarray experiments generate long lists of genes with altered expression, the interpretation of these data depends on the judgment of the investigator performing the experiment (Bustin et al., p. 269, 2nd full paragraph). Additionally, a comparison of the same microarray experiment performed a few weeks apart can demonstrate a lack of reproducibility (p. 269, 2nd full paragraph). For instance, a comparison of 47 and 98 genes identified from independent studies to be associated with metastasis does not reveal a single gene in common (Bustin et al. pg 269-270). Additionally, the expression data derived from a cDNA microarray are not the endpoint in a study, but merely deliver several candidate genes whose function require further verification (Bustin et al., abstract; p. 271, col 1, 1st full paragraph). The PRO1287 gene and polypeptide have *not* been associated with tumor formation or the

development of cancer, nor have they been shown to be predictive of such. No mutation or translocation of PRO1287 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1287 is expressed in corresponding normal tissues, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that PRO1287 mRNA is amplified in a variety of samples and invites the artisan to determine the significance of this increase.

Applicant presents a declaration by Dr. Polakis filed with the response under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1287 in tumor samples relevant to normal samples.

Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 1-8, and 11-13 based upon 35 U.S.C. §§ 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicant discusses the declaration by Dr. Ashkenazi submitted with the response under 37 CFR 1.132. Dr. Ashkenazi states that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification.

Dr. Ashkenazi states that if gene amplification results in overexpression of the mRNA and the corresponding gene product, then it identifies that the gene target is important in cancer therapy. However, the instant specification does not disclose any correlation of the corresponding protein level of PRO1287 in normal stomach and kidney tumor in comparison to stomach tumor and normal kidney samples, respectively. Only gene expression data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 1-8, and 11-13 based upon 35 U.S.C. §§ 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Applicants present Hanna and Morning reference that teaches that HER-2/neu gene has been shown to be amplified and/or overexpressed in 10-30% of invasive breast cancers. However, the specification teaches amplification of PRO1287 from a pool of cDNA library. The specification does not teach how many tumor samples (stomach or kidney) were compared with normal samples. There is no statistical significance and numbers were presented that one skill of the art can use in predicting an association of PRO1287 to a tumor.

Applicants argue that the higher expression of the PRO1287 gene in normal stomach and kidney tumor tissue compared to stomach tumor and normal kidney tissue, respectively, are real and significant, thus the claimed antibodies that bind the PRO1287 polypeptides have utility as cancer diagnostic tools. The declaration of J. Christopher Grimaldi teaches that the DNA libraries used in the gene expression studies

were made from pooled samples of normal and of tumor tissues. Grimaldi states in section 6 in previously submitted declaration that "I conducted a semi-quantitative analysis of the expression of the DNA sequences of interest in normal versus tumor tissues. Expression levels were graded according to a scale of +, -, and +/- to indicate the amount of the specific signal detected. Using the widely accepted technique of PCR, it was determined whether the polynucleotides tested were more highly expressed, less expressed, or whether expression remained the same in tumor tissue as compared to its normal counterpart. Because this technique relies on the visual detection of ethidium bromide staining of PCR products on agarose gels, it is reasonable to assume that any detectable differences seen between two samples will represent at least a two fold difference in cDNA."

The declaration of Dr. Grimaldi does not teach the level of reproducibility or the level of reliability of the results. There are no relative or absolute levels of PRO1287 mRNA in control or tumor tissue disclosed. Neither the specification nor the declarations provide any evidence that indicates what the differences were or if they were statistically significant. If a clinician took a stomach or kidney tissue sample from a patient with stomach or kidney cancer, for example, what is the likelihood that when compared with a stomach cancer or normal kidney, respectively, the level of PRO1287 from the patient would be higher? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual? Would a universal normal control be necessary or would a normal tissue matched sample be a sufficient control for comparison?

Applicants have provided no indication of the nature or number of samples that were used. The only thing Applicants teach is that PRO1287 mRNA was "overexpressed" in kidney cancer or "underexpressed" in stomach cancer, and this does not enable the skilled artisan to differentiate between expression levels in order to diagnose any diseases. 2) Regarding the strength of opposing evidence, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue (for example, Hu et al. 2003, Journal of Proteome Research 2:405-412, of record). Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary. The "universal normal control" in the specification is disclosed as a pooled epithelial cell sample comprising epithelial cells from liver, kidney and lung. This pooled control sample is not a proper control for determining whether a gene is overexpressed in a diseased tissue relative to a normal, matched tissue is (e.g., lung tumor vs. normal lung sample) because specific tissues such as liver, kidney, lung, and colon express different genes at different levels. For instance, Saito-Hisaminato et al (DNA Res., 9:35, 2002) demonstrate that among 23,040 genes studied in *normal* human tissue, 4080 genes were highly expressed (greater than 5-fold higher than in other tissues) in one or only a few tissues (see abstract, lines 3-5). This represents about 18% of the total genes tested. Further, a cluster analysis that grouped tissues based on similarity of gene expression showed that lung was not at all similar to kidney or liver (see figure 2, page 40), which are all

mixed together in the instant "universal control." Saito-Hisaminato et al. only disclose genes that are highly expressed in one tissue compared to other tissues (i.e. greater than 5-fold difference). A 5-fold difference is greater than the difference required to establish that a gene is 'overexpressed' or 'differentially expressed' by comparison in the specification. In the instant application, there are no relative or absolute expression levels. With respect to the instant "universal control," according to Saito-Hisaminato et al (Figure 1, adding up the uniquely expressed genes for kidney, liver and lung), the combination of liver, kidney and lung as a control would result in about 600 highly expressed genes that would not reasonably be expressed in an appropriate control, such as normal matched tissue. Also, an equally confounding problem of using the wrong tissue for comparison is the absence of or diminished expression of a gene in a particular tissue type. Accordingly, this would artificially increase or decrease the magnitude of differences observed in the instant microarray as well. Thus, Hu et al. and Saito-Hisaminato et al. constitute strong opposing evidence. 3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Grimaldi is employed by the assignee and is an inventor in this application. 4) Finally, with regard to the presence or absence of factual support for the expert's opinion, it is noted that while the declaration Dr. Grimaldi discusses findings in terms of "a majority of cases", no data, percentage increases or levels of significance are disclosed, making it difficult for the Examiner independently to draw conclusions. Also, no published work of other researchers using a universal normal control has been cited. Based on consideration of the totality of the evidence, it is proper to maintain the rejections.

Claim Rejections - 35 USC § 112-lack of enablement

The rejection of claims 1-8, 11-13 under 35 U.S.C. 112, first paragraph is maintained for reasons of record on p. 4 Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

35 USC § 112-first paragraph - enablement

The rejection of claims 1-8, 11-13 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for the reasons of record.

Applicants' arguments have been fully considered but have not been found to be persuasive. Being overexpressed in normal stomach or kidney tumor samples compare to stomach tumor or normal kidney tissue respectively is not a functional limitation. Even if the specification provided support for diagnosing stomach or kidney tumor samples with PRO1287, the skilled artisan would not know how to use polypeptide sequences having sequences at least 80, 90, 95%, or 99% sequence identity to PRO1287 for diagnosing stomach or kidney tumor. Similarly, one skilled in the art would not know how to engineer a sequence such that it is overexpressed in certain tissues.

35 USC § 112-first paragraph – written description

The rejection of claims1-8, 11-13 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement, is maintained for reasons of record on p. 6-7 of paper mailed on 6/25/2004.

Applicants argue that the claims have been amended to provide that the claimed polypeptides are more highly expressed in normal stomach, or kidney tumor samples compare to stomach tumor or normal kidney universal control tissues, respectively. Thus, Applicants argue that based on the detailed description of the cloning and expression of native variants of PRO1287 in the specification, the description of the gene amplification assay, the actual reduction to practice of sequences SEQ ID NO: 71 that encodes the polypeptide of SEQ ID NO: 72, and the functional recitation in the instant claims, one skilled in the art would know that Applicants possessed the subject matter of the pending claims.

Applicant argues that, based on the detailed description of the cloning and expression of variants of PRO1287 in the specification, the description of the gene amplification assay and description of testing the ability of test variant polypeptides in the assay, the actual reduction to practice of PRO1287 and the functional recitation in the instant claims, Applicants submit that one of skilled in the art would know that Applicants possessed the invention as claimed in the instant claims. This has been fully considered but is not found to be persuasive. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d

1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In the instant case, only one polypeptide sequence has been identified with a *potential* link to cancer as recited in the claims. No other species have been disclosed. One species is not adequately representative of the many sequences encompassed by the claims. As stated above, the claims have no functional limitations. In addition, the specification does not provide a utility or function for PRO1287. The claimed polypeptides may have functions and structures which differ greatly from that of PRO1287, therefore one of skill in the art would not be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later

than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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18 November 2005
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